08031801

6673986

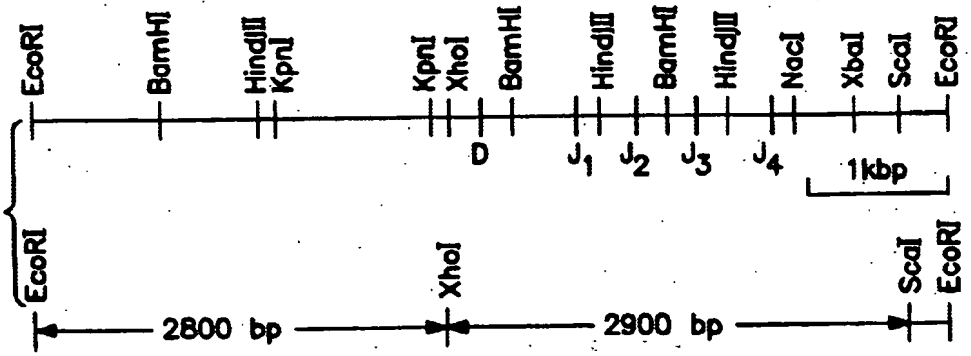


FIG. IA

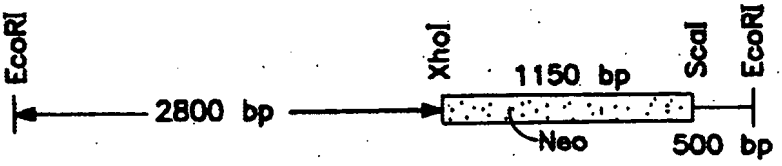


FIG. IB

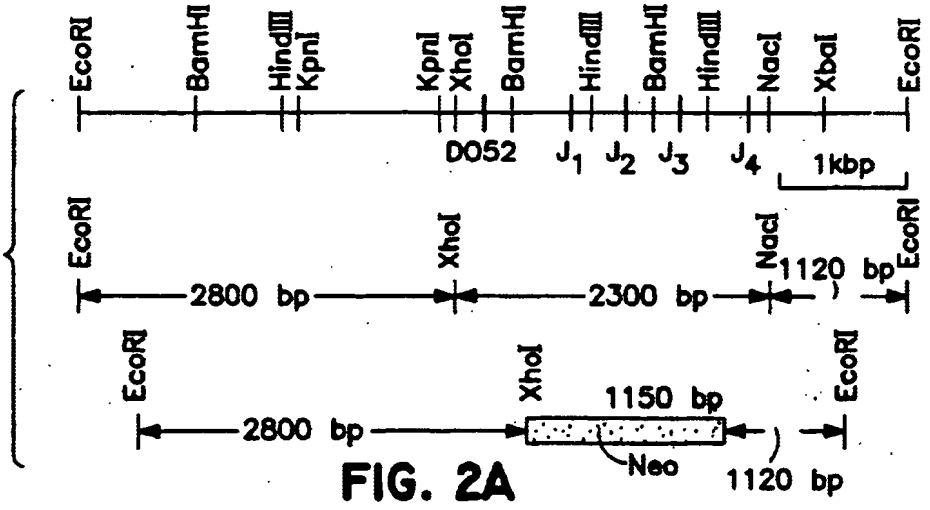


FIG. 2A

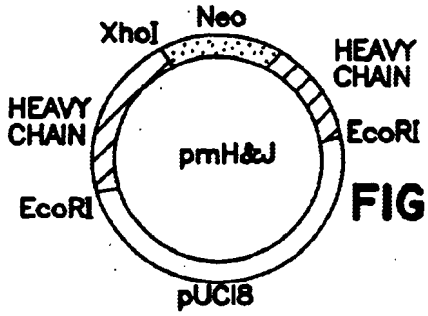


FIG. 2B

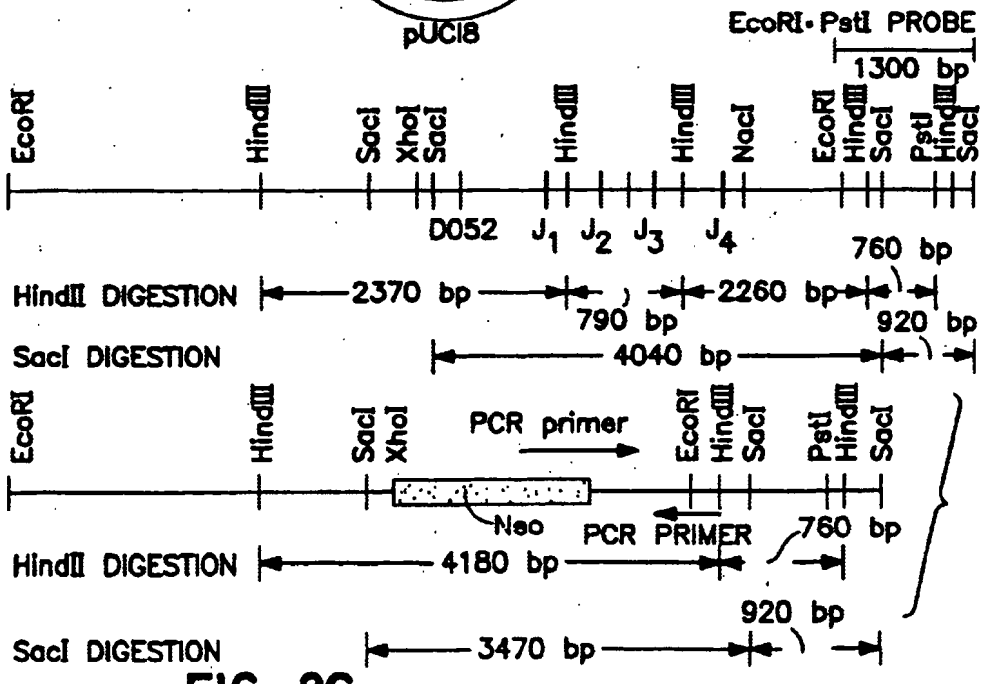


FIG. 2C

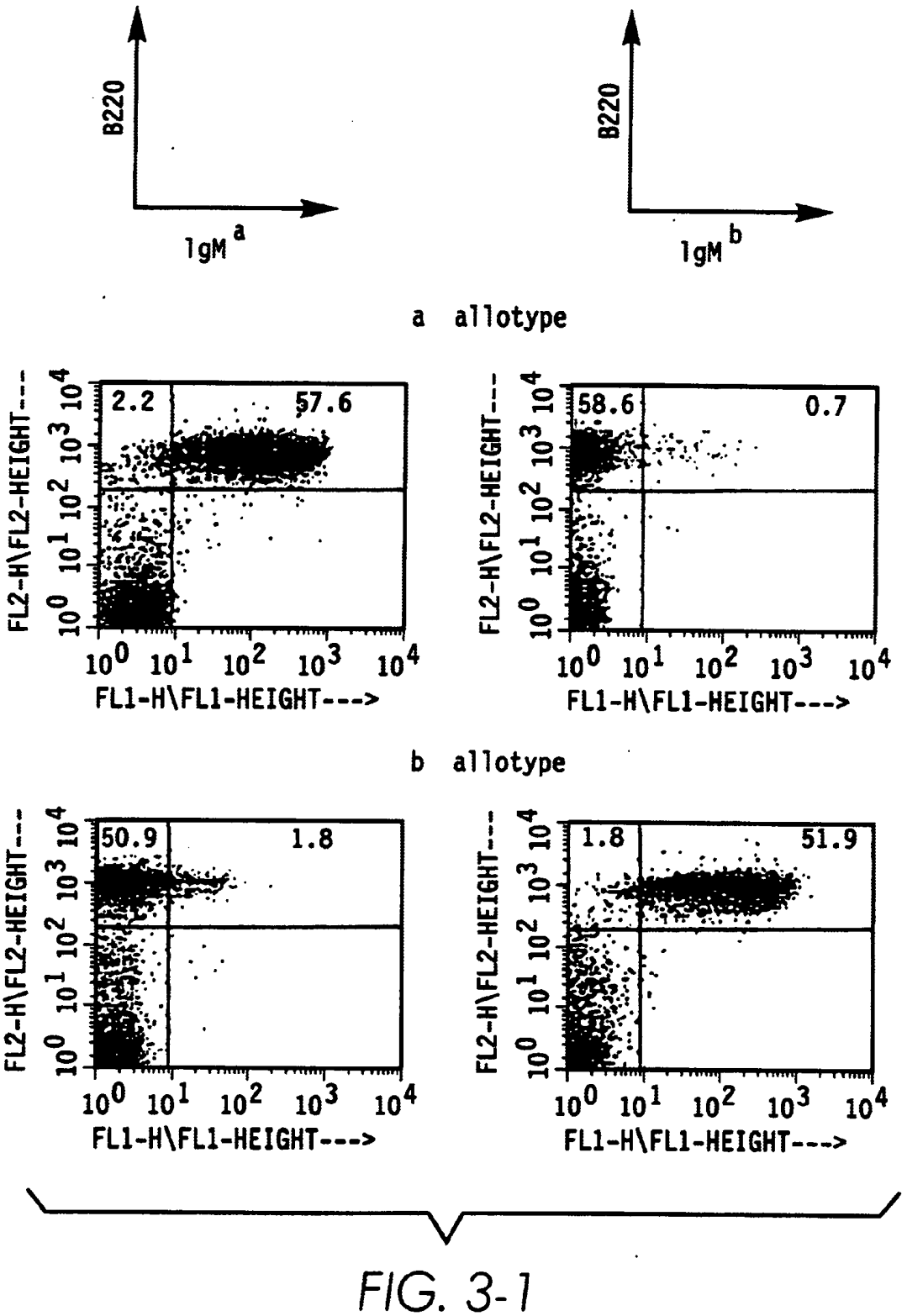


FIG. 3-1

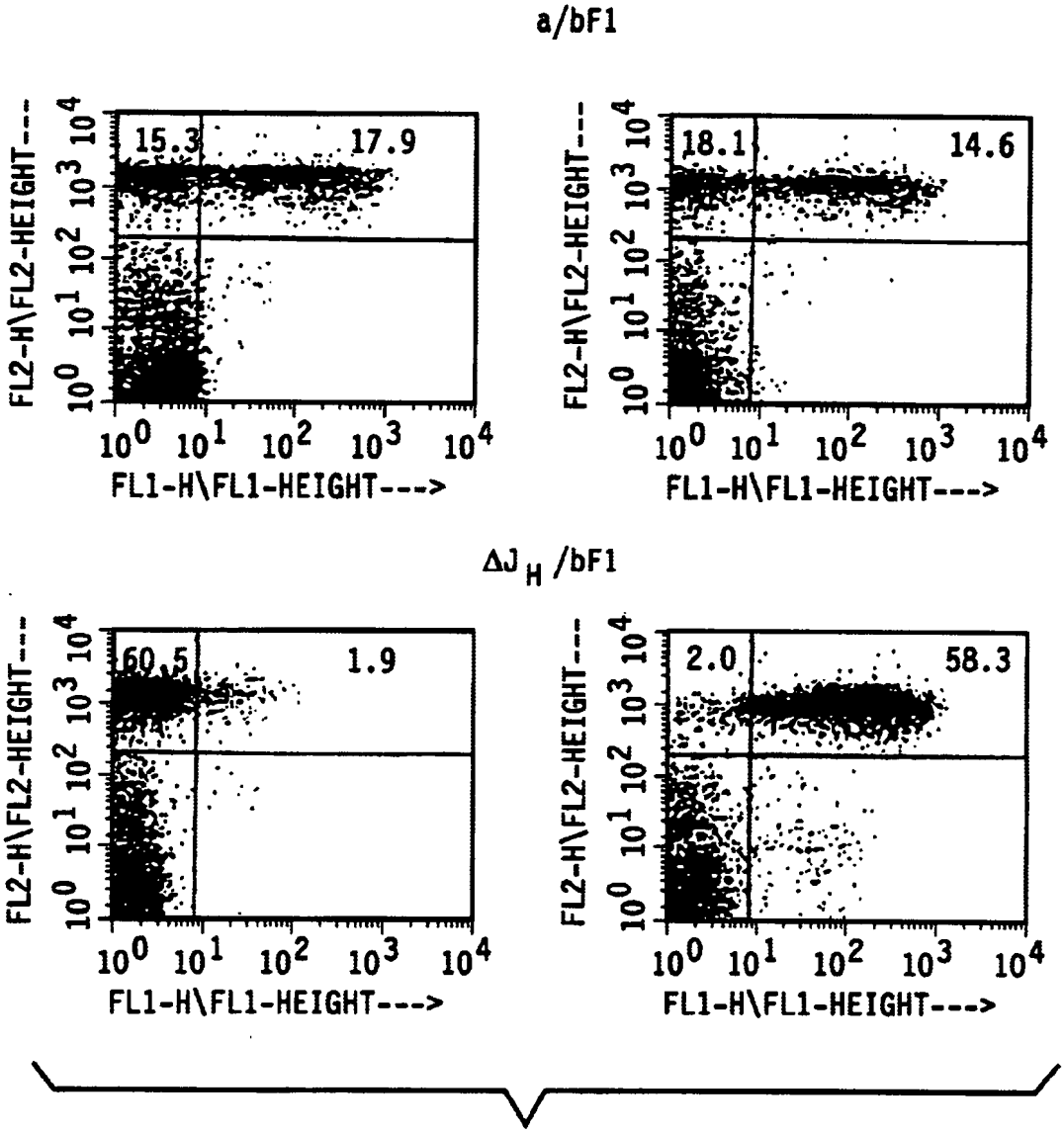


FIG. 3-2

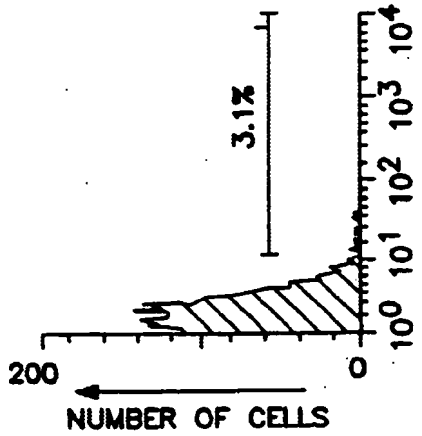


FIG. 4C

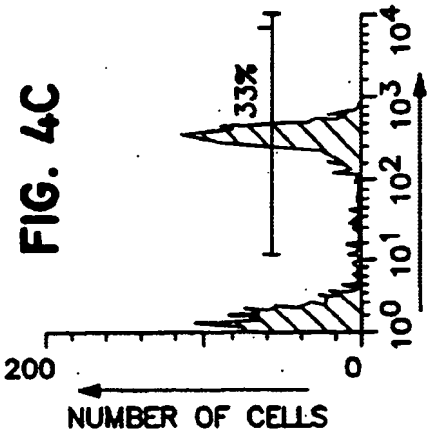


FIG. 4F

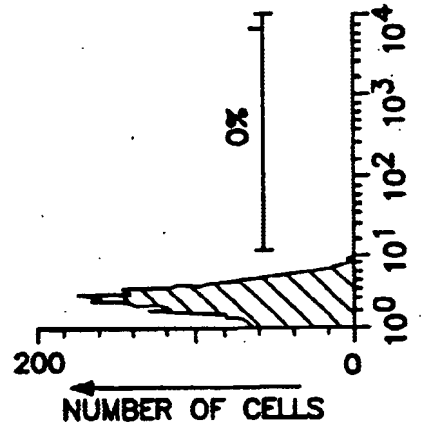


FIG. 4B

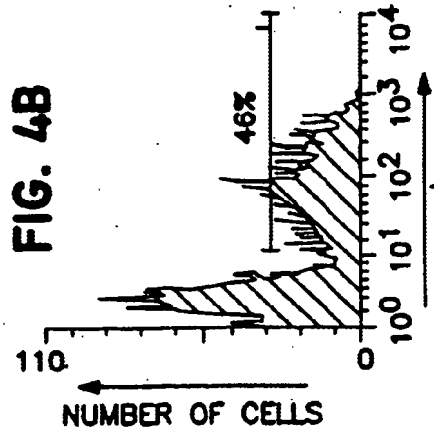


FIG. 4E

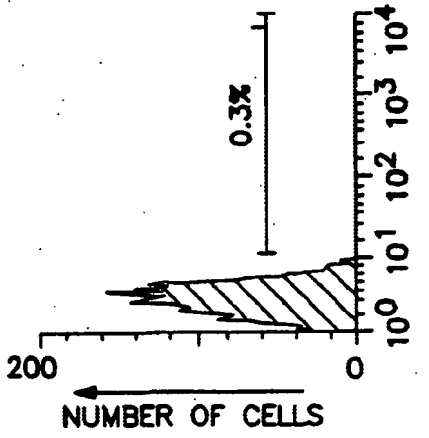


FIG. 4A

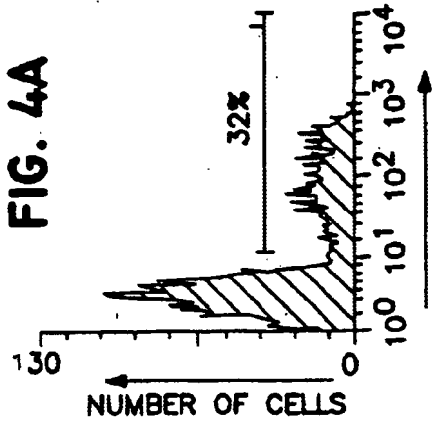


FIG. 4D

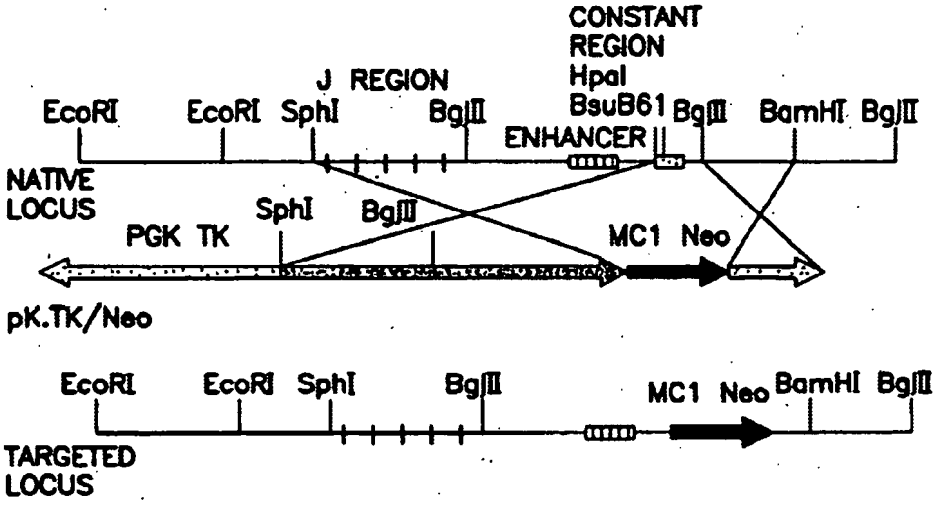


FIG. 5

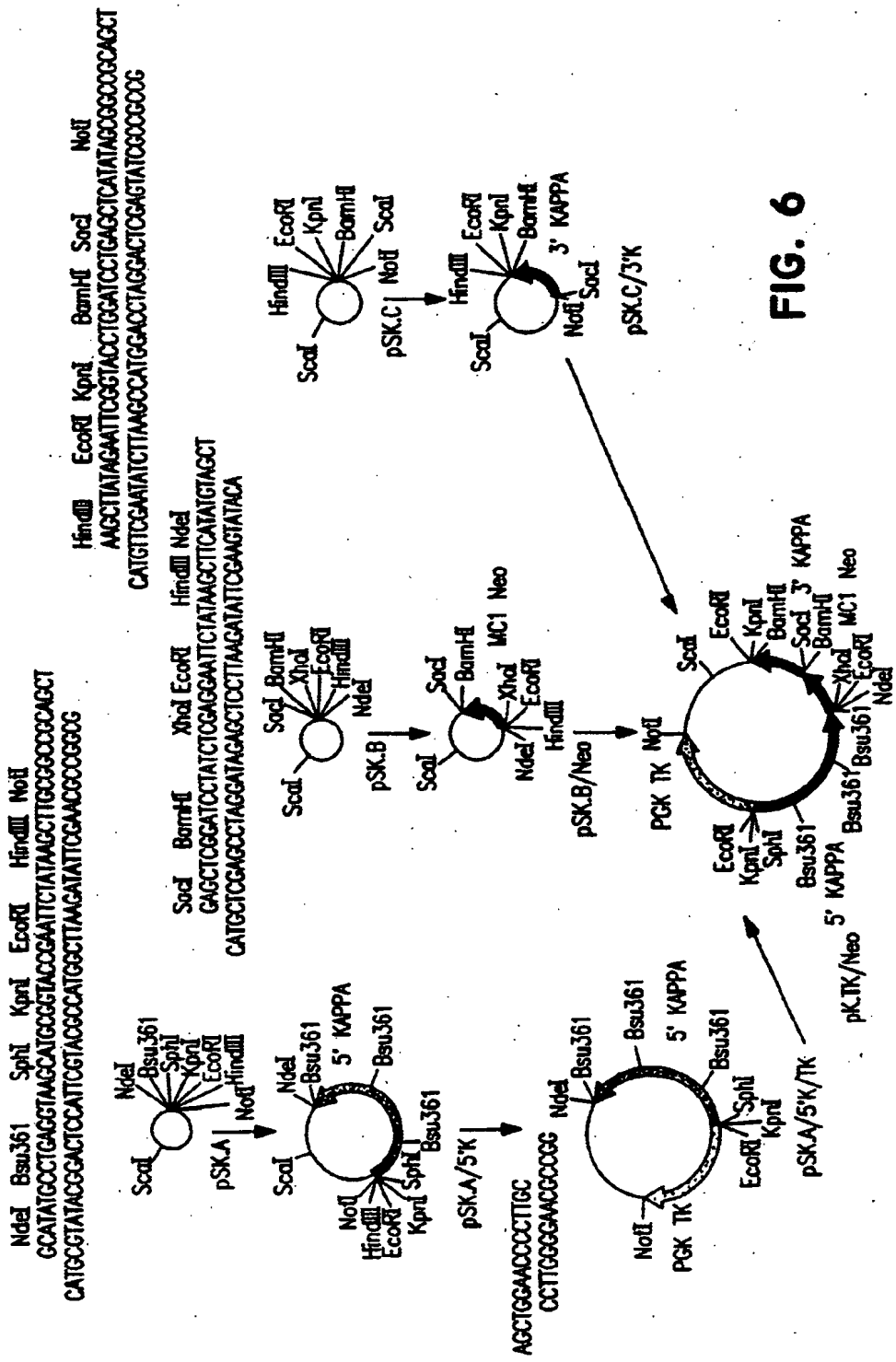


FIG. 6

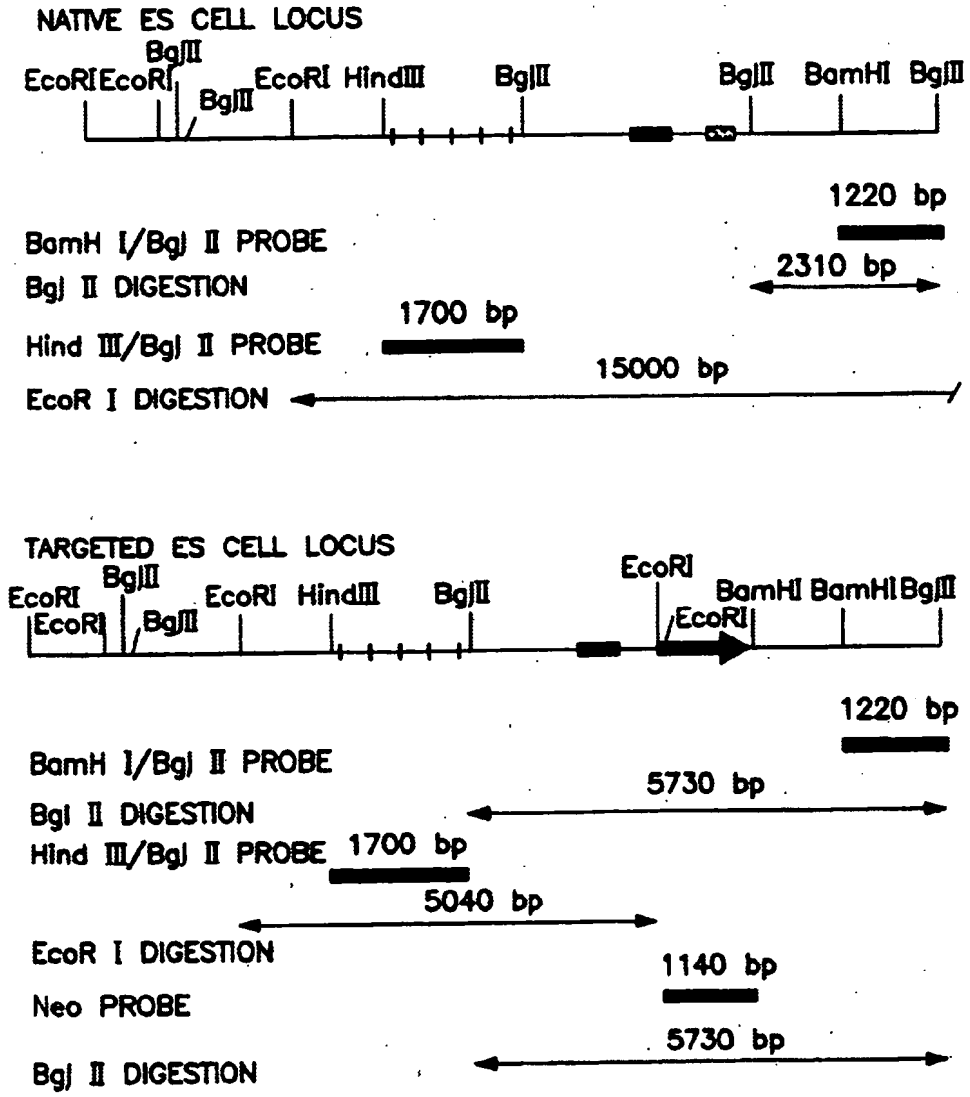


FIG. 7

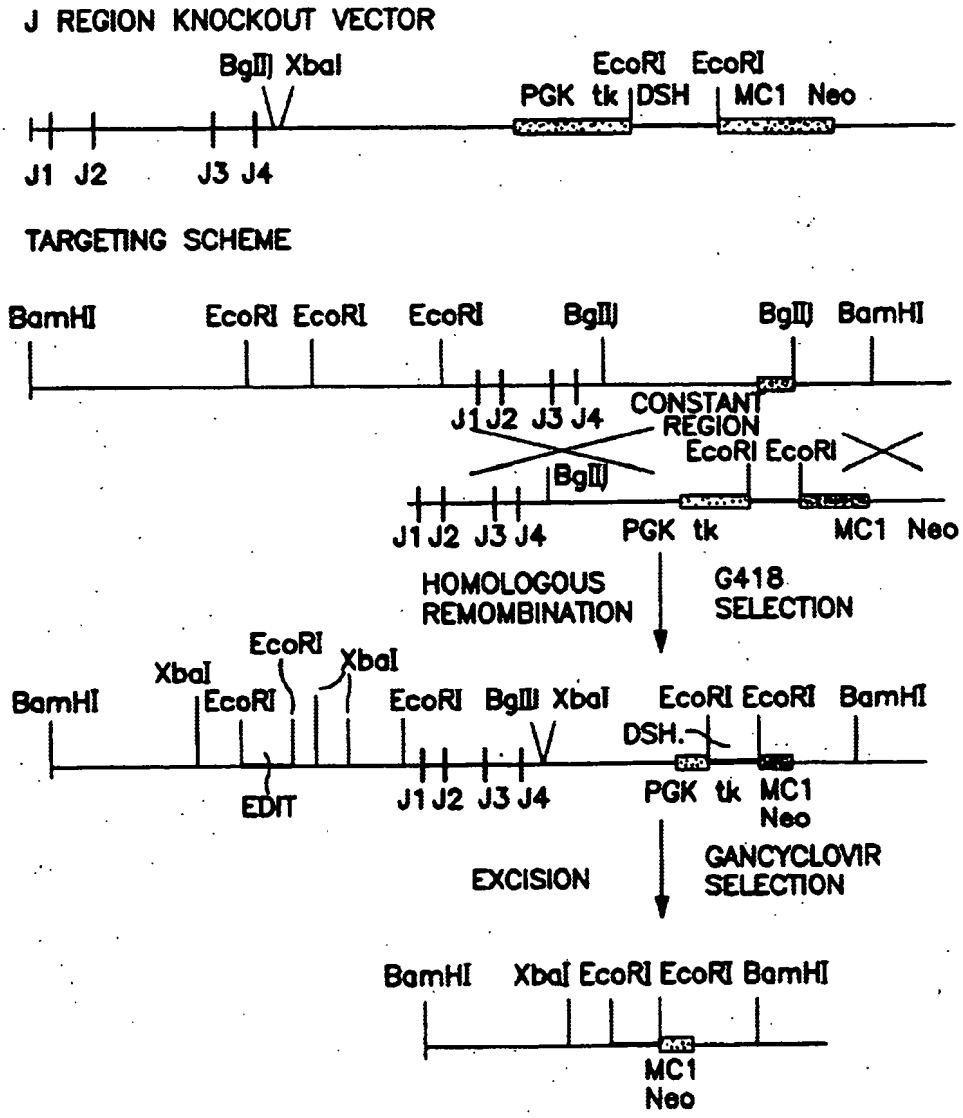


FIG. 8

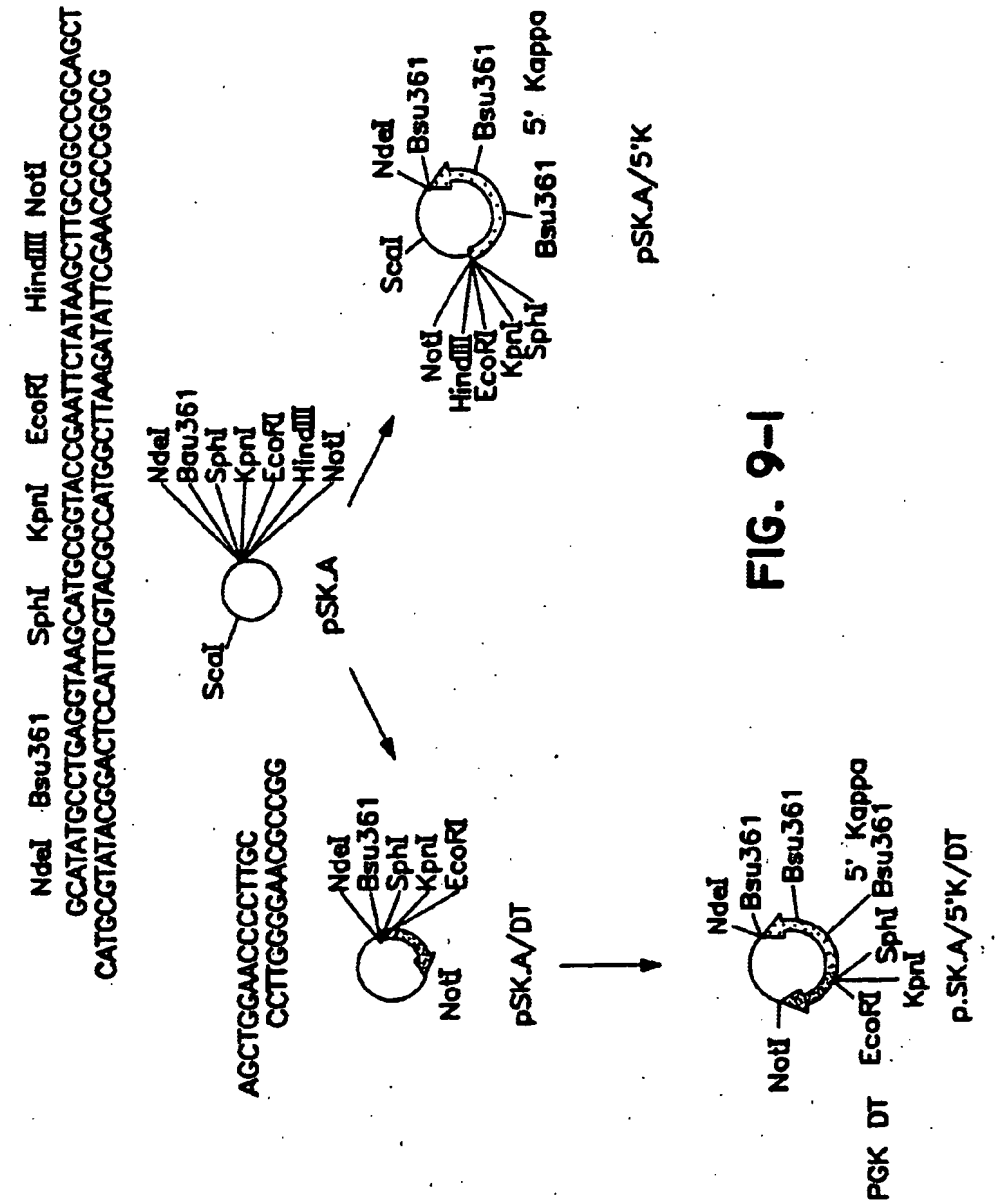


FIG. 9-I

SacI BamHI XhoI EcoRI HindIII NdeI
GAGCTCGGATCCTATCTCGAGGAATTCTATAAGCTTCATATGTAGCT
CATCCTCGAGCCTAGGATAGAGCTCCTTAAGATATTCGAAGTATACA

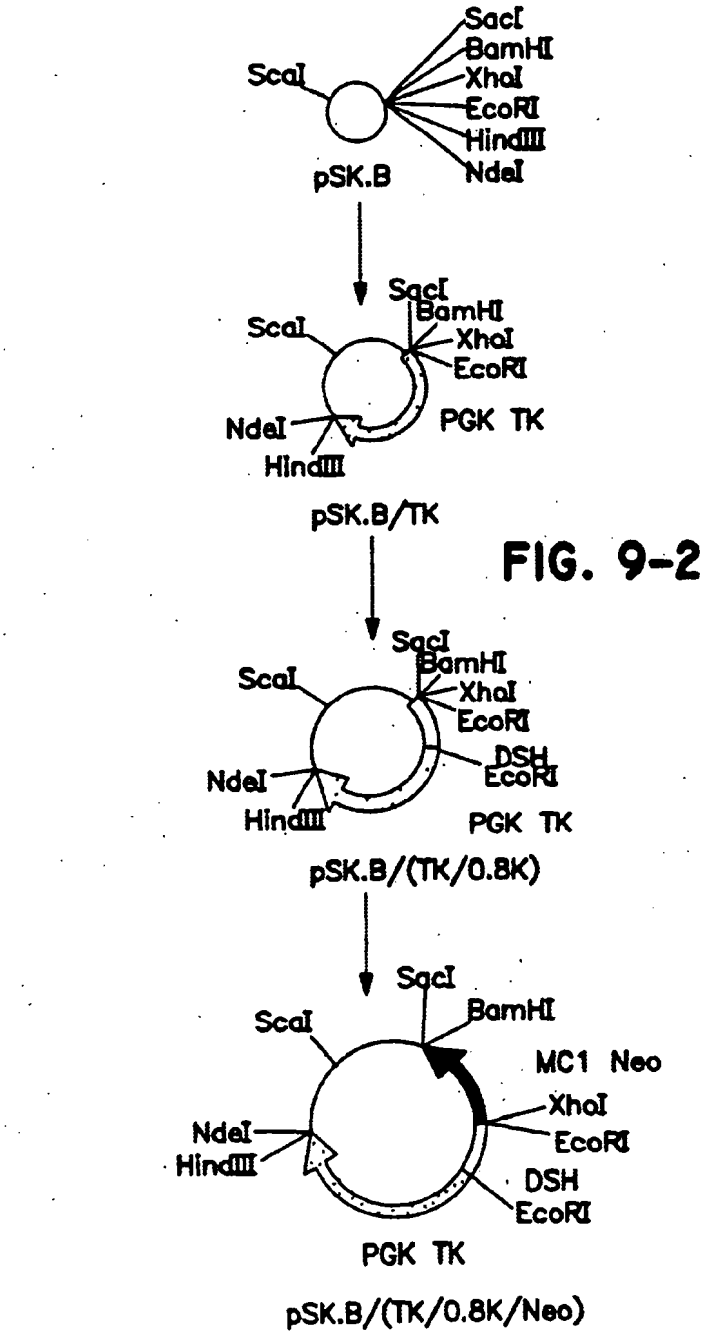


FIG. 9-2

HindIII EcoRI KpnI BamHI SacI NotI
AAGCTTATAGAATTCGGTACCTGGATCCTGAGCTCATAGCGGCCGCAGCT
CATGTTCGAATATCTTAAGCCATGGACCTAGGACTCGAGTATCGCCGGCG

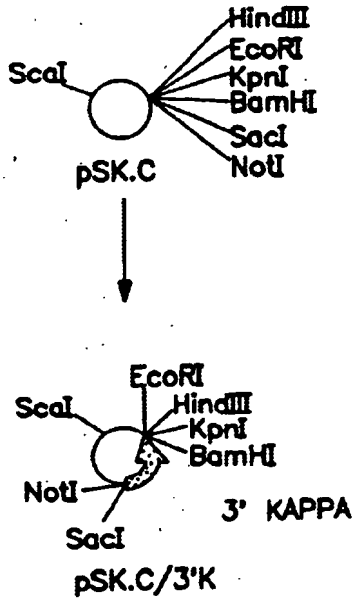
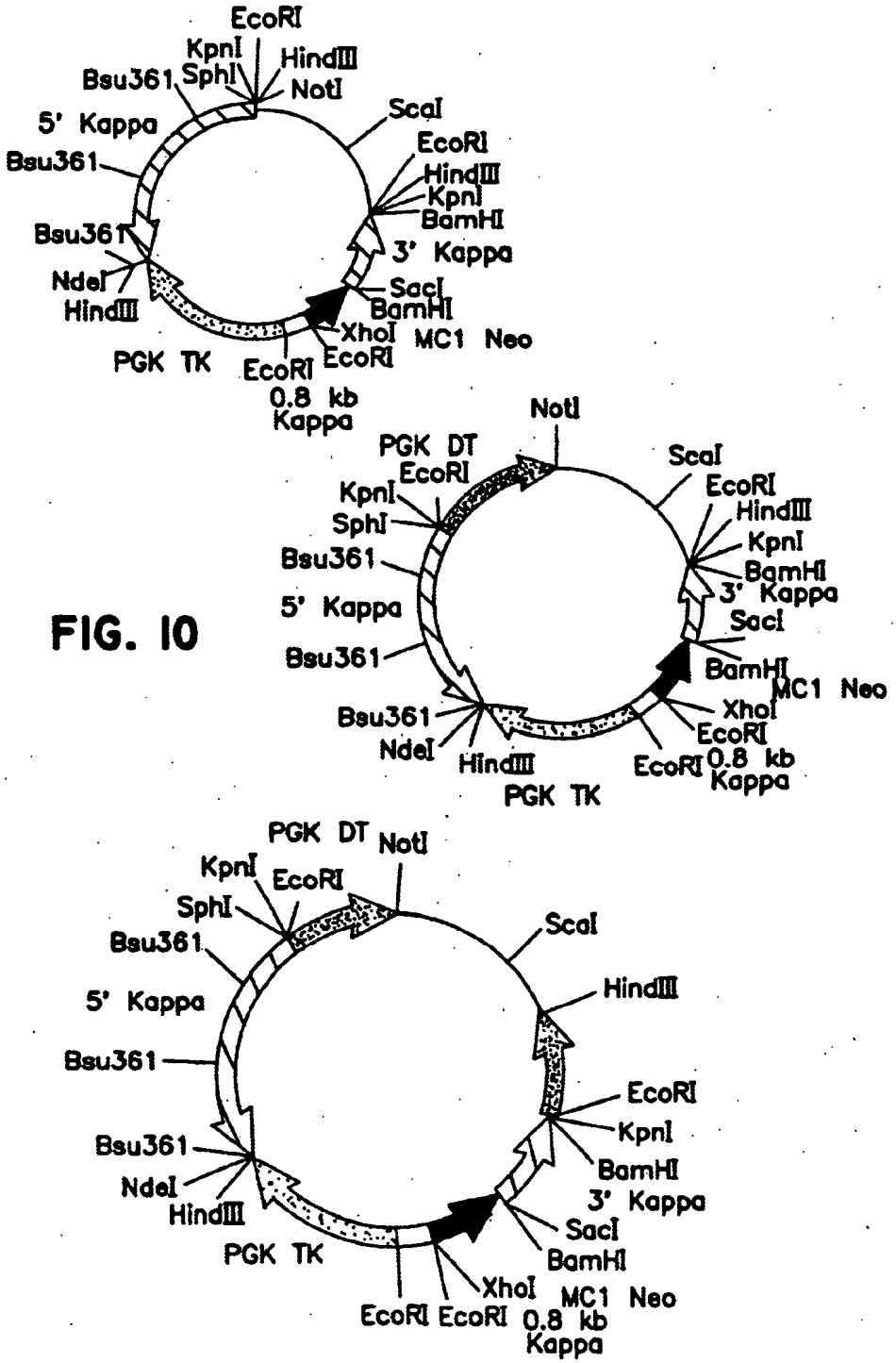


FIG. 9-3

FIG. 10



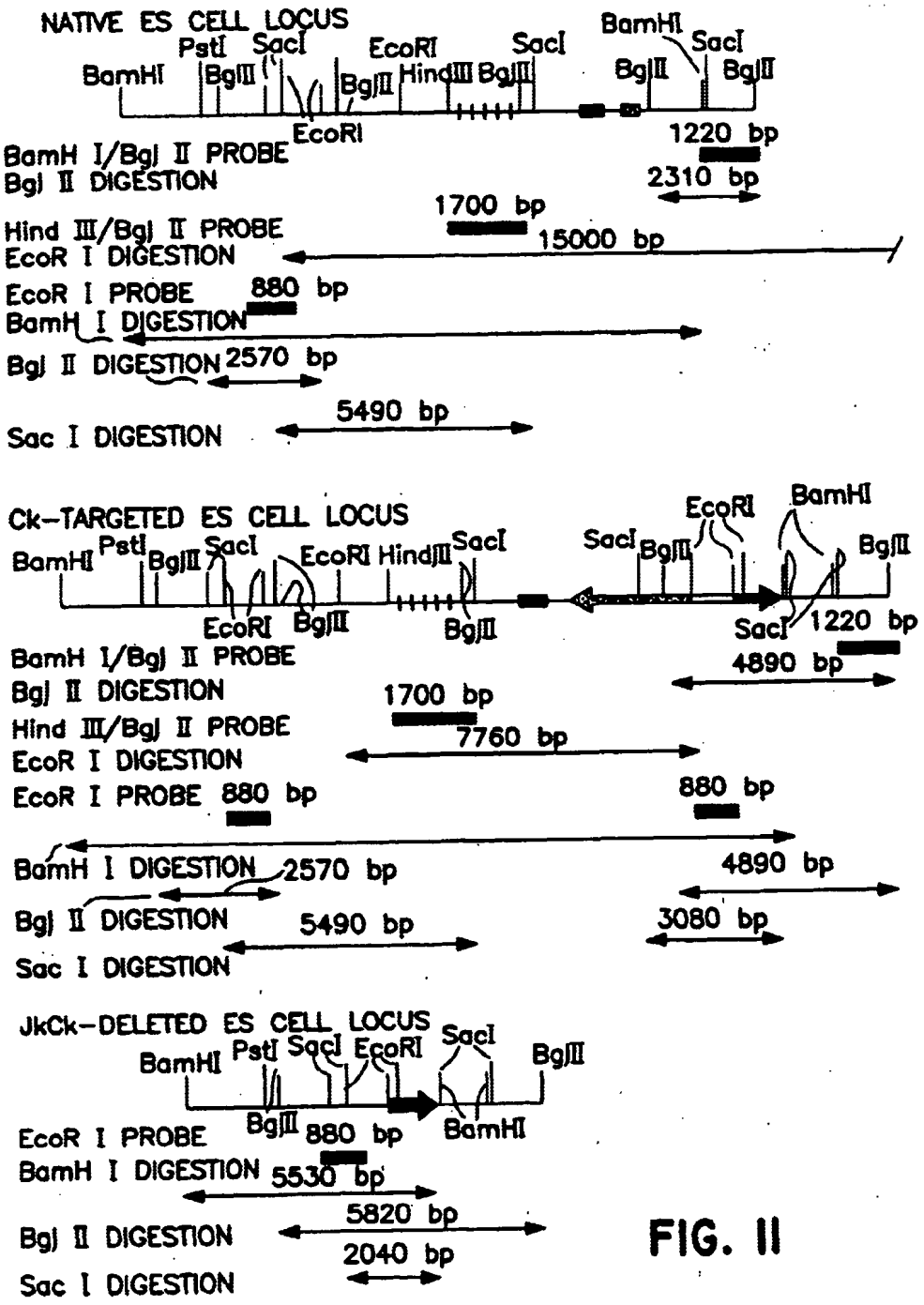


FIG. 11

FIG. 12A

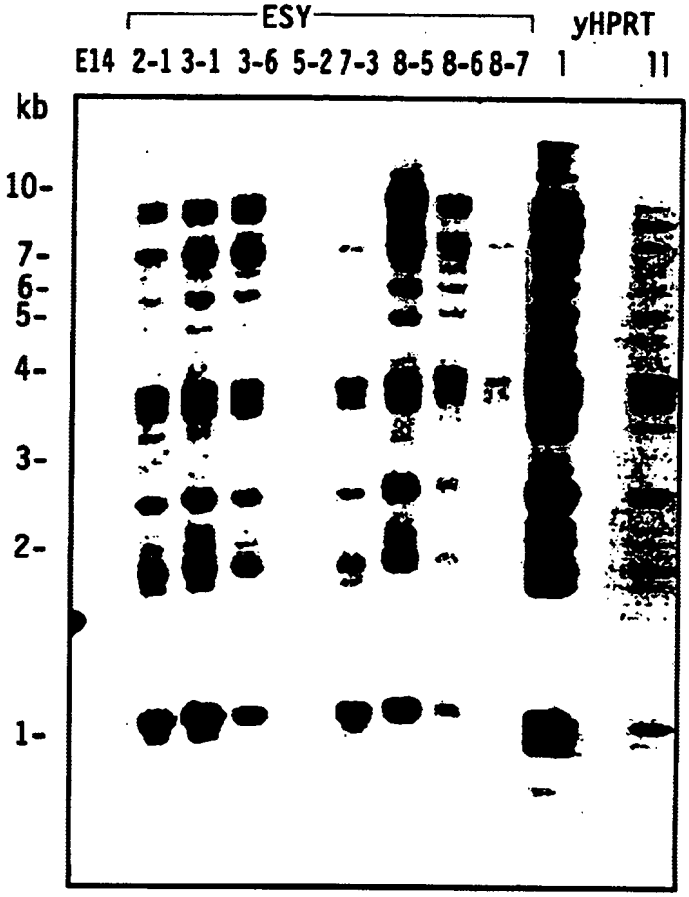


FIG. 12B

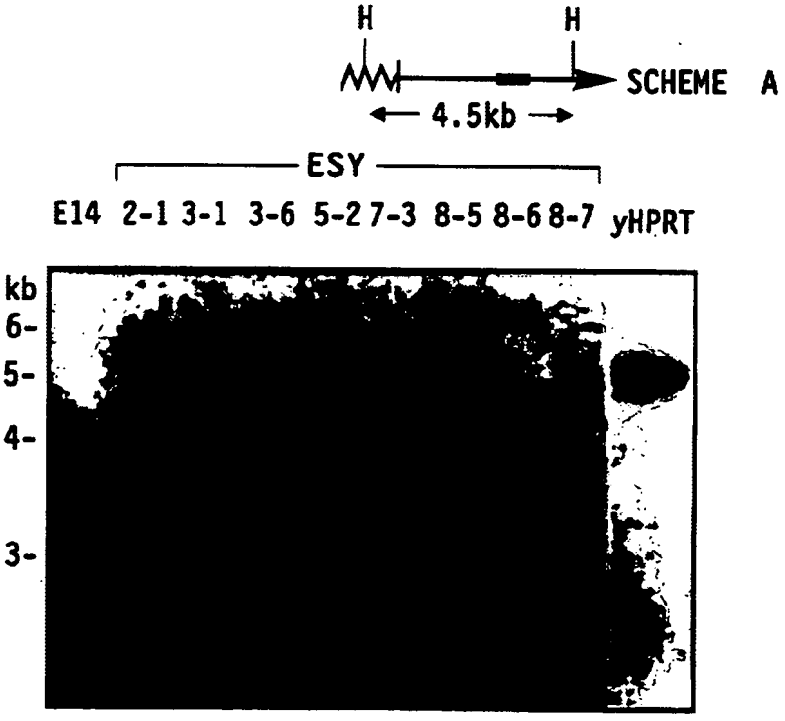
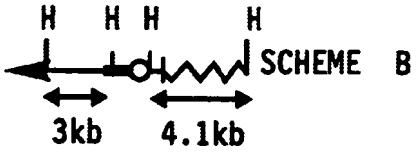


FIG. 12C



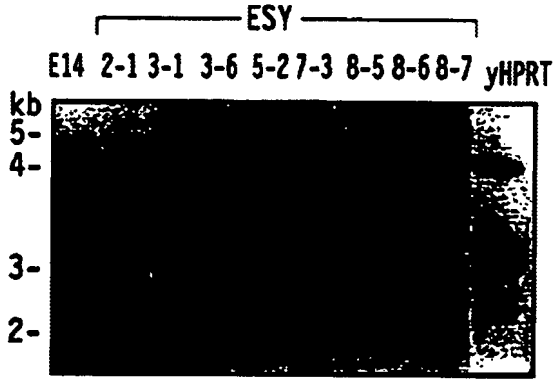


FIG. 12D

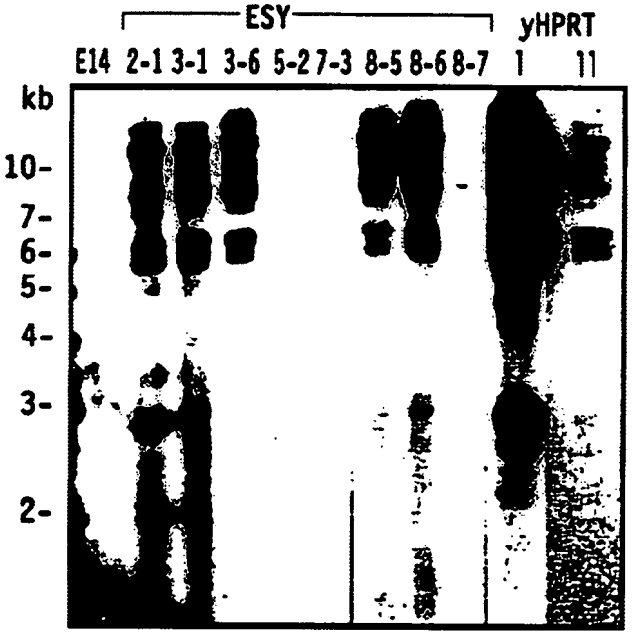


FIG. 12E

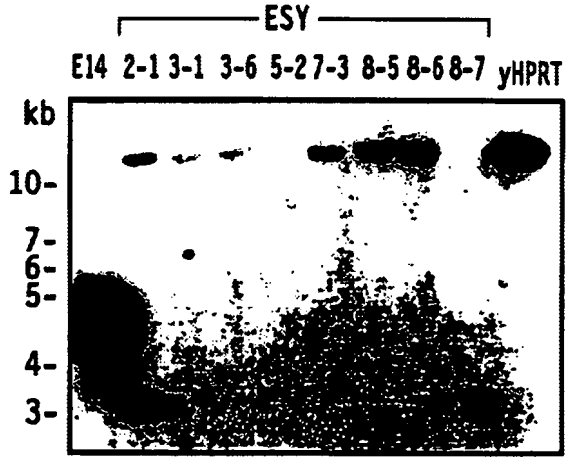


FIG. 13A

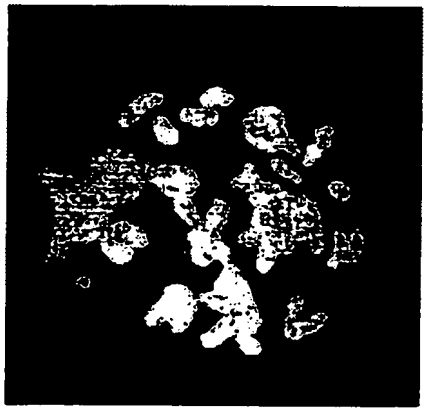


FIG. 13B

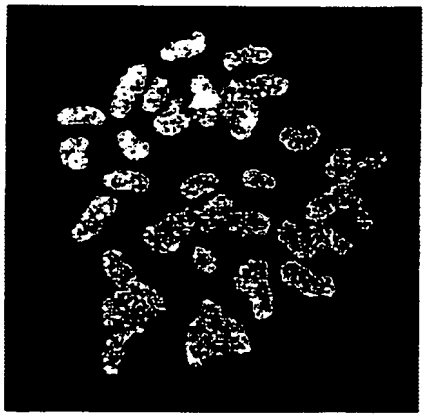


FIG. 13C

FIG. 13D

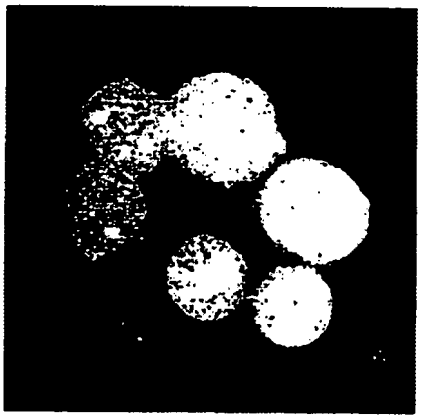


FIG. 14A

FIG. 14B

FIG. 14C

FIG. 14D

FIG. 14E

FIG. 14F

FIG. 14I

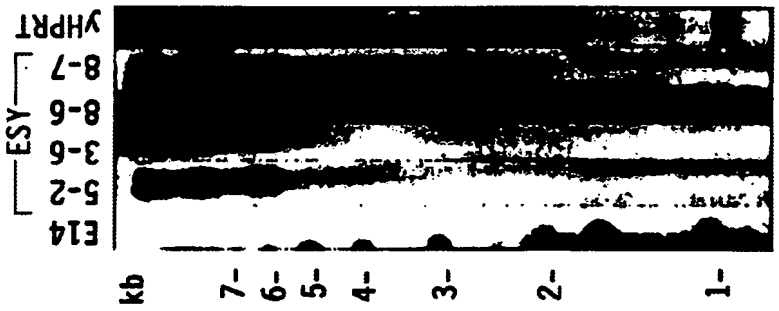


FIG. 14H

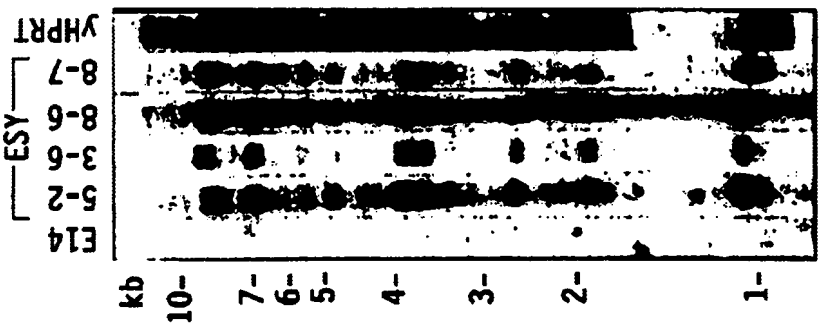


FIG. 14G

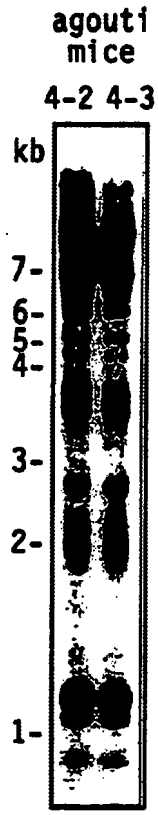


FIG. 14J

FIG. 14K

FIG. 15A

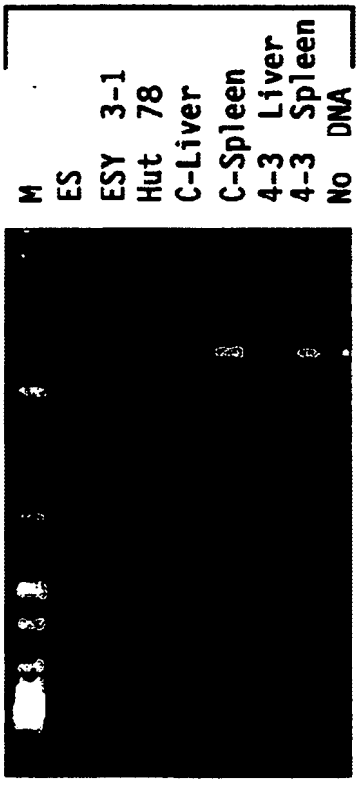
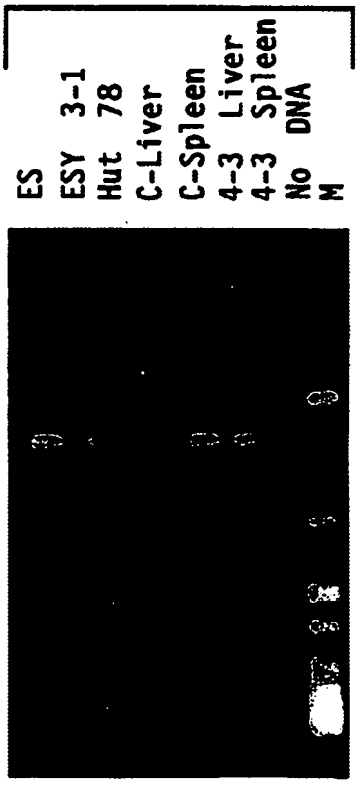


FIG. 15B



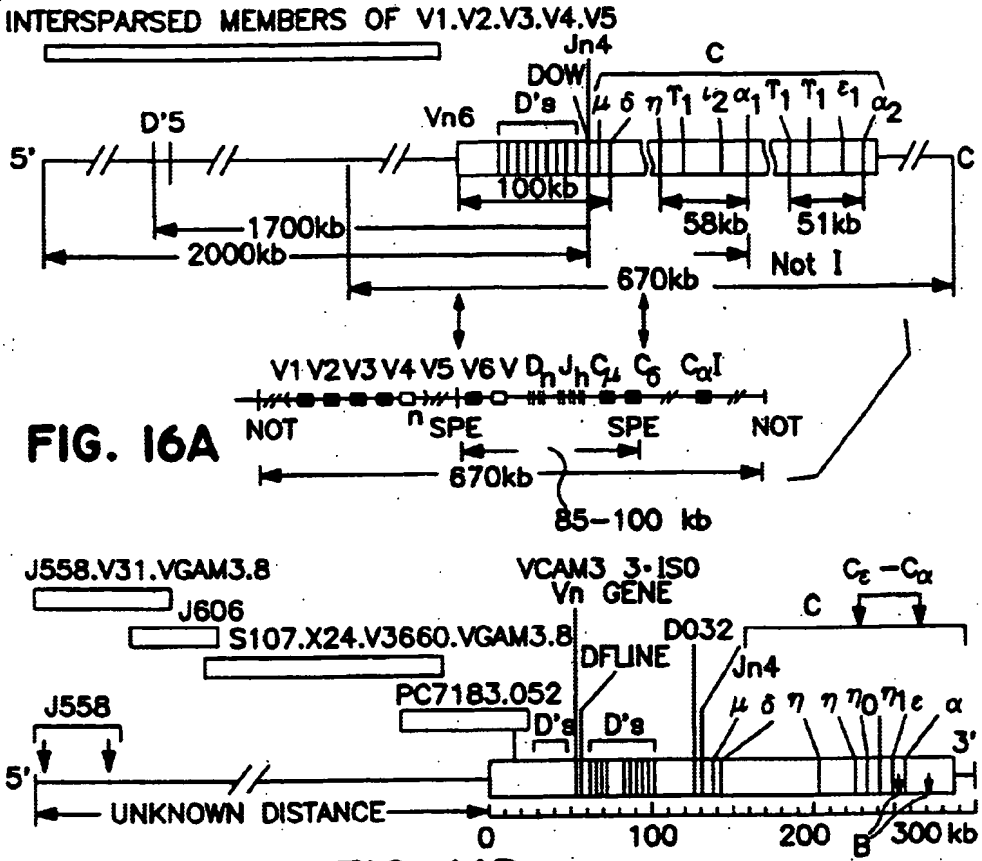


FIG. 16A

FIG. 16B

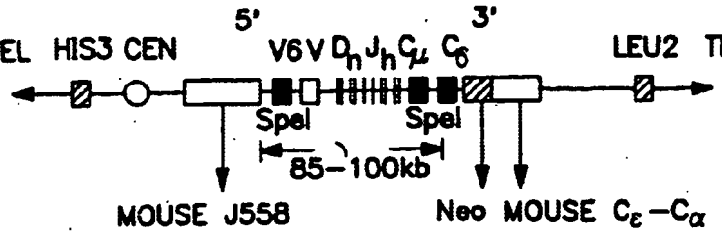


FIG. 16C

Mouse Breeding Scheme

Cross IA.

heterozygous inactive Murine IgH
X
heterozygous inactive Murine IgK

$\frac{\text{MIgH (inactive)}}{\text{MIgH}}$ $\frac{\text{MIgK}}{\text{MIgK}}$
X
$\frac{\text{MIgH}}{\text{MIgH}}$ $\frac{\text{MIgK (inactive)}}{\text{MIgK}}$

↓

F1 (cross I A)

$\frac{\text{MIgH (inactive)}}{\text{MIgH}}$ $\frac{\text{MIgK (inactive)}}{\text{MIgK}}$

Cross IB.

heterozygous Human IgH
X
heterozygous Human IgK

$\frac{\text{MIgH}}{\text{MIgH}}$ $\frac{\text{MIgK}}{\text{MIgK}}$ $\underline{\text{HIgH}}$
X
$\frac{\text{MIgH}}{\text{MIgH}}$ $\frac{\text{MIgK}}{\text{MIgK}}$ $\underline{\text{HIgK}}$

↓

F1 (cross I B)

$\frac{\text{MIgH}}{\text{MIgH}}$ $\frac{\text{MIgK}}{\text{MIgK}}$ $\underline{\text{HIgH}}$ $\underline{\text{HIgK}}$

Cross II. F1 (cross I A) x F1 (cross I B)

↓

F2 Quadruple Heterozygotes

$\frac{\text{MIgH (inactive)}}{\text{MIgH}}$ $\frac{\text{MIgK (inactive)}}{\text{MIgK}}$ $\underline{\text{HIgH}}$ $\underline{\text{HIgK}}$

Cross III. Intercross F2 mice

↓

F3 DOUBLE Homozygotes

$\frac{\text{MIgH (inactive)}}{\text{MIgH (inactive)}}$ $\frac{\text{MIgK (inactive)}}{\text{MIgK (inactive)}}$ $\underline{\text{HIgH}}$ $\underline{\text{HIgK}}$

FIG. 17

MAMMALIAN HOST GENOTYPES FIG. 18A

	Hetero- or Hemi-zygous Mice	Intercross Product Mice *
I.	$\frac{\Delta mIgL}{mIgL}\ \frac{mIgH}{mIgH}$	$\frac{\Delta mIgL}{\Delta mIgL}\ \frac{mIgH}{mIgH}$
II.	$\frac{mIgL}{mIgL}\ \frac{\Delta mIgH}{mIgH}$	$\frac{mIgL}{mIgL}\ \frac{\Delta mIgH}{\Delta mIgH}$
III.	$\frac{mIgL}{mIgL}\ \frac{mIgH}{mIgH}\ hIgH$	$\frac{mIgL}{mIgL}\ \frac{mIgH}{mIgH}\ \frac{hIgH}{hIgH}$
IV.	$\frac{mIgL}{mIgL}\ \frac{mIgH}{mIgH}\ hIgL$	$\frac{mIgL}{mIgL}\ \frac{mIgH}{mIgH}\ \frac{hIgL}{hIgL}$
V.	Animal I X Animal II	
	$\frac{\Delta mIgL}{mIgL}\ \frac{mIgH}{\Delta mIgH}$	$\frac{\Delta mIgL}{\Delta mIgL}\ \frac{\Delta mIgH}{\Delta mIgH}$
VI.	Animal III X Animal V	
	$\frac{mIgL}{\Delta mIgL}\ \frac{mIgH}{\Delta mIgH}\ hIgH$	$\frac{\Delta mIgL}{\Delta mIgL}\ \frac{\Delta mIgH}{\Delta mIgH}\ \frac{hIgH}{hIgH}$ and $\frac{\Delta mIgL}{\Delta mIgL}\ \frac{\Delta mIgH}{\Delta mIgH}\ hIgH$
VII.	Animal IV X Animal V	
	$\frac{mIgL}{\Delta mIgL}\ \frac{mIgH}{\Delta mIgH}\ hIgL$	$\frac{\Delta mIgL}{\Delta mIgL}\ \frac{\Delta mIgH}{\Delta mIgH}\ \frac{hIgL}{hIgL}$ and $\frac{\Delta mIgL}{\Delta mIgL}\ \frac{\Delta mIgH}{\Delta mIgH}\ hIgL$
VIII.	Animal VI X Animal VII	
	$\frac{\Delta mIgL}{\Delta mIgL}\ \frac{\Delta mIgH}{\Delta mIgH}\ hIgL\ hIgH$	$\frac{\Delta mIgL}{\Delta mIgL}\ \frac{\Delta mIgH}{\Delta mIgH}\ \frac{hIgL}{hIgL}\ \frac{hIgH}{hIgH}$
	$\frac{mIgL}{\Delta mIgL}\ \frac{mIgH}{\Delta mIgH}\ hIgL\ hIgH$	$\frac{\Delta mIgL}{\Delta mIgL}\ \frac{\Delta mIgH}{\Delta mIgH}\ \frac{hIgL}{hIgL}\ \frac{hIgH}{hIgH}$ and $\frac{\Delta mIgL}{\Delta mIgL}\ \frac{\Delta mIgH}{\Delta mIgH}\ hIgL\ hIgH$

Applicants: [redacted]iu Kucherlapati et al. Docket No.: Cell 4.4 CPA
Application No. [redacted]031,801 Filed: March 15, 1993 Confirmation No.: 194
For: GENERATION OF XENOGENEIC ANTIBODIES
Agent: R. Mirako Puzdera, Reg. No. 46,984 Sheet 24 of 24

IX. Animal III X Animal IV

$\frac{mIgL}{mIgL}$ $\frac{mIgH}{mIgH}$ $\frac{hIgL}{\cdot}$ $\frac{hIgH}{\cdot}$ $\frac{mIgL}{mIgL}$ $\frac{mIgH}{mIgH}$ $\frac{hIgL}{hIgL}$ $\frac{hIgH}{hIgH}$

X. Animal II X Animal IX

$\frac{mIgL}{mIgL}$ $\frac{\Delta mIgH}{mIgH}$ $\frac{hIgL}{\cdot}$ $\frac{hIgH}{\cdot}$ $\frac{mIgL}{mIgL}$ $\frac{\Delta mIgH}{\Delta mIgH}$ $\frac{hIgL}{hIgL}$ $\frac{hIgH}{hIgH}$ and $\frac{mIgL}{mIgL}$ $\frac{\Delta mIgH}{\Delta mIgH}$ $\frac{hIgL}{hIgL}$ $\frac{hIgH}{hIgH}$

XI. Animal I X Animal IX

$\frac{\Delta mIgL}{mIgL}$ $\frac{mIgH}{mIgH}$ $\frac{hIgL}{\cdot}$ $\frac{hIgH}{\cdot}$ $\frac{\Delta mIgL}{\Delta mIgL}$ $\frac{mIgH}{mIgH}$ $\frac{hIgL}{hIgL}$ $\frac{hIgH}{hIgH}$ and $\frac{\Delta mIgL}{\Delta mIgL}$ $\frac{mIgH}{mIgH}$ $\frac{hIgL}{hIgL}$ $\frac{hIgH}{hIgH}$

---

*Not all possible genotypes from intercrosses are shown.

Δ = functionally inactive locus
m = mouse endogenous gene
h = human transgene
IgH = immunoglobulin heavy chain
IgL = immunoglobulin light chain

FIG. 18B